REMARKS

Claims 1-12, 14-15, 17-18 and 20-21 are currently pending in the application. Claims 1-12, 14-16 and 20 are cancelled. Claims 17, 18 and 21 are currently amended. Claims 22 - 40 are added.

In the interest of clarity, new claims 22-40 are replacements for claims 1-12 and 14-16.

The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Rejection of Claims 1-12, 14-15, 17-18 and 20-21 Under 35 U.S.C. §112, 1st paragraph ("Enablement")

Claims 1-12, 14-15, 17-18 and 20-21 were rejected under 35 U.S.C. §112, first paragraph for lack of enablement.

The Office Action states:

--The first and second polypeptides are not provided in a form that comprise any of the recited covalent modifications and therefore do not enable the reversal of any one of the covalent modifications recited in the claims. –

The Office Action further states:

-- Enzymatic action and covalent modification of either the first or second polypeptides would not take place in thc absence of the functional group used to modify.--

The Office Action concludes that:

--the detection of thc presence of a modifying enzyme is not enabled in the absence of the modifying group being present in the sample which would provide for the association of the first and second polypeptides.--

and that,

--The first and second polypeptides are not provided in a form that comprise any of the recited covalent modifications and therefore do not enable the reversal of any one of the covalent modifications recited in the claims.--

As discussed in the Examiner interview of October 21, 2003, claim 1 has been replaced by two new claims 22 and 23 herein, directed to methods of detecting a) covalent modification and b) reversal of covalent modification of a polypeptide pair, respectively.

Applicants submit that claim 22, which is directed to a method of detecting covalent modification of the polypeptide pair by a modifying enzyme now requires the presence of a 'modifying agent substrate' (step b).

Applicants further submit that claim 23, which is directed to a method of detecting reversal of covalent modification of the polypeptide pair by a modifying enzyme now requires that the second binding partner polypeptide be covalently modified.

Applicants submit that new claims 22 and 23 are enabled for the detection of a modifying enzyme. Applicants therefore respectfully request the withdrawal of the rejection under §112, first paragraph.

Rejection of Claim 12 Under 35 U.S.C. §112, 1st paragraph ("Enablement")

Claim 12 is rejected under 3S U.S.C. 112, first paragraph, for lack of enablement.

The Office Action states:

> -- Claim 12 recites a combination of claim limitations the sets forth an antibody that binds to either the first or second polypeptides, and not the association of the first and second polypeptides based upon the covalently modified combination of the first and second polypeptides..--

Claim 12 is cancelled and replaced by new claims 34 and 35. Applicants submit that claims 34 and 35 require that the association between the immobilized first polypeptide and the second, binding partner polypeptide is measured using an antibody that binds to the second, binding partner polypeptide after the second, binding partner polypeptide has bound to the first polpeptide. Applicants submit that support for the use of an antibody that binds to the second, binding partner polypeptide can be found on page 22, line 29 that states:

--Association of binding partners may be measured by:

> Mass: monitor increase in molecular mass of the hybrid species (e.g. use surface plasmon resonance)
> Radioactivity: monitor radiolabelled binding partner (e.g. use phosphorimager or photosensitive emulsion) monitor either radiolabelled partner (e.g. use scintillation proximity assay)
> Fluorescence: e.g., binding partner is labelled fluorescently: measurefluorescence directly e.g., use two different fluorophores, one on each of the polypeptides: measure FRET between two fluorescent polypeptides
> **Immunology: e.g., use labelled antibody to the binding partner**— (emphasis added)

Because the method of claims 34 and 35 requires that the steps of each claim occur in sequence, Applicants submit that antibody binding to the second, binding partner polypeptide occurs after the binding of the second, binding partner polypeptide to the immobilized first polypeptide and thus would not interfere with the binding of the first polypeptide to the second, binding polypeptide. Applicants therefore submit that the rejection as applied to claim 12 does not apply to new claims 34 and 35.

Applicants submit that claims 34 and 35 are enabled for the detection of a modifying enzyme using an antibody that binds to the second, binding partner polypeptide. Applicants therefore respectfully request the withdrawal of the rejection under §112, first paragraph.

Rejection of Claims 4 and 20 Under 35 U.S.C. §112, 2nd paragraph ("Indefiniteness)"

Claims 4 and 20 are rejected under 35 U.S.C. §112, 2nd paragraph for being indefinite. The Office Action states that:

> --Claim 4 defines the presence of two labels and depends from claim 3 recites the phrase "a label" and amended claim 1 that only measures the association. --

Applicants submit that claim 4 is cancelled without prejudice. Applicants submit that cancelled claims 2, 3, 4, 5 and 10 are replaced with new claims 24, 27, 28, 25 and 26, respectively. New claim 24, which corresponds to cancelled claim 4, recites "wherein at least

one of the polypeptides is labeled". Thus, Applicants submit that all limitations of this claim find proper antecedent basis in claims 22 or 23 from which it depends.

The Office Action further states that:

> --Claim 20 broadens the scope of claim 1 by reciting the phrase "an enzymatic modification"—

Applicants submit that the cancellation of claim 20 renders this rejection moot.

In view of the above, Applicants submit that the rejection of claims 4 and 20 under 35 U.S.C. §112, 2nd paragraph is moot and request the withdrawal of the rejection.

Branch et al. (U.S. 6,235,466):

The Examiner has previously noted the Branch et al. reference as presenting a potential prior art issue (noted in Office Action mailed May 8, 2003 and in the interview of October 21, 2003). Applicants submit that the Branch et al. reference uses an anti-phosphotyrosine antibody to detect the phosphorylation of a protein tyrosine kinase enzyme. Applicants note that the claims presently presented for examination specifically require that the second, binding partner polypeptide is not a phospho-specific antibody. Support for this language is found on page 2 of the specification, which states:

> "Other types of modification which have in the past been monitored include phosphorylation. This may often be monitored in a manner analogous to the monitoring of ubiquitin, using phosphorylation-specific antibodies to immunoprecipitate and/or immunoblot only phosphorylated form(s) of the protein. However, the raising of phospho-specific antibodies is an expensive proposition, requiring careful screening of large numbers of different antisera. Moreover, the production of such reagents, even if attempted, is not always possible. For example, there is simply no reliable antibody available for the detection of phospho-serine or phospho-threonine. Currently, the only way of detecting these phosphorylation events is either to embark upon a programme to raise context-specific anti-phospho-antisera, which is not always feasible, or to use radioactive labelling techniques in conjunction with standard immunoprecipitation, assuming that immunoprecipitating antibodies are available to the protein

> which is to be tested. Clearly, it is simply not possible to use radioactive labelling when dealing with human patients. ……..
>
> "*The present invention seeks to overcome such difficulties.*"
>
> (specification page 2, lines 7-19 and 27; emphasis added)

The specification thus clearly teaches away from the use of phospho-specific antibodies in the methods described and claimed, thereby providing support for the recited language.

In view of the above, Applicants submit that the claims are allowable over the Branch et al. reference.

CONCLUSION

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,

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